THE DIAGNOSIS OF CANCER OF THE STOMACH.[1]

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In all efforts at treatment of cancer of the stomach we are confronted by two relentless facts, which limit our knowledge and ability. One is of a negative and the other is of a positive nature. The first barrier consists in the fact that we do not know what carcinoma is. We do not understand the nature of malignant neoplasms. The second is, that no matter what our methods of treatment, regardless of at how early a date, or with what skill it is executed, the cases treated will eventually and inevitably suffer from a recurrence of the disease. This is an actual fact in 99 per cent. of all gastric cancers that have undergone operation. With such a state of our knowledge, we are condemned to one of three courses. Either we merely go on to do things just as our fathers did, and for no better reasons than because they did them so, or, trusting to some personal authority, we adopt at random the recommendation of some specific in a speculative hope that it may answer; or, lastly,—and this seems the most favorable case,—we ourselves attempt to improve upon certain processes and methods hitherto employed. This improvement may follow as a result of accumulated experience, arranged, corrected, and amplified by master minds; or it may be the result of experimental investigation.

In our present knowledge of malignant neoplasms, the analytical mind remains in the presence of phenomena the causes of which are hidden from it. But these causes are capable of being discovered and understood, just as the cause of tuberculosis and of diphtheria was at one time unknown to us, and has been shown to be capable of discovery.

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The only diagnosis that can be of interest to a surgeon is an EARLY diagnosis. I have prefaced my remarks in the manner stated in order to emphasize the difficulty of an early diagnosis of any disease the cause of which is unknown, and which does not give prompt and unmistakable clinical manifestations. Many of us can recall the difficulty in the diagnosis of tuberculosis, diphtheria, and malaria prior to the discovery of the specific organisms which were proven to be the causes of these diseases.

Definition of the Term "Early Diagnosis."—The nature and concept of an early diagnosis of carcinoma of the stomach is intimately associated with a knowledge of the *duration* of the disease, which can be approximately, though not definitely, ascertained by three methods: (1) Observing the rate of growth of carcinomas in organs that are open to direct inspection (the uterus, rectum, mammary glands, etc.); (2) by noting the size and rate of growth after the beginning of the subjective and objective complaints in tumors (especially gastric tumors) capable of palpation, and (3) by noting the rate of growth in visible or palpable metastases. Cancer of the stomach may occur and run its entire course in a latent form. Osler and McCrae (*Philadelphia Medical Journal*, February 3, 1900) report seven such cases, in all of which I fail to find any statement referring to chemical and microscopical analysis of the gastric contents. It is true the gastric symptoms were not prominent. These cases show that in cases of obscure or doubtful diagnosis, chemical and microscopical analyses of the gastric contents should be considered as indispensable as the analysis of the urine in similar cases. But latent cancer has been discovered at the autopsy in my own experience, in cases in which frequent chemical analysis of the gastric contents had been made. This occurred in two cases of cancers that arose from gastric ulcers, and in which the secretion of hydrochloric acid continued to the end of life, and none of the classical signs and symptoms of gastric carcinoma were evident during the clinical history. Such cases, however, are exceedingly rare, and, in my opinion, cases of latent cancer of the stomach will be reported less and less, the more gastric test-meal analysis is undertaken in obscure cases, and the more such analysis is raised to the importance which urinary analysis occupies.

To revert to the duration of the disease, this naturally must vary with the histological nature of the neoplasm. Some neoplasms, such as the scirrhus or the colloid carcinoma, grow rather slowly, and also form metastases slowly. From statistics relating to the results of operation, it is evident that these two neoplasms are also the most favorable to operation (Hemmeter, "Diseases of the Stomach," Section on Surgery, second edition, page 355). On the other hand, the medullary or the adeno or epithelial carcinoma grow more rapidly. In my experience, carcinoma of the stomach has, as a rule, a latent period of three to four months, in which it does not give the classical symptoms of gastric cancer, but clandestinely progresses under the guise of a chronic gastritis or nervous dyspepsia. This is an important period for the clinician. An early diagnosis means the recognition of gastric cancer during these three or four months, when he is confronted with nothing but the symptoms of chronic gastritis or nervous dyspepsia. Such a diagnosis is unfortunately only rarely possible. The first and main obstacle in the way is the indolence and procrastination of the patient, and sometimes, unfortunately, also of the practitioner in charge. The second obstacle is found in the fact that the methods necessary to effect such a diagnosis which are thus far available, are time-robbing, require great patience and persistence, and a knowledge of chemistry and microscopic technique, only exceptionally met with, or capable of application in general practice. Later on I will formulate a number of guiding principles, however,—as much as has so far crystallized out of the study and investigation concerning the clinical history of cancer, which might serve the practitioner as a criterion, at what time such cases of chronic gastritis or nervous dyspepsia should be transferred to the surgeon. But I should like to premise what I shall have to say concerning the chemical and histological technique of the early diagnosis, by stating that the simple continuance of a chronic gastritis or nervous dyspepsia in spite of logical and scientific treatment, accompanied with progressive loss of body weight, during three to four weeks—these two factors alone justify the suspicion of a latent gastric carcinoma.

The ingenuity, immense amount of investigation and indefatigable perseverance which have been bestowed upon the chemical and histological methods of diagnosis of gastric carcinoma cannot but excite universal admiration. But in my experience they are of no greater help to the clinician for the recognition of this disease than the simple continuance or even aggravation of a chronic gastritis and progressive loss of body weight (though every other symptom and sign may be lacking) in spite of proper treatment.

In the following I will consider seriatim the various clinical methods employed for the detection and recognition of carcinoma of the stomach. I will employ the right of the conservative clinician, viz., the critical faculty of determining the actual value of these aids and the deduction of practical conclusions from their association.

Age.—According to the tables of Brinton, 600 cases, Welch, 2075 cases, and Haberlin, 11,424 cases, three-fourths of all cases of gastric cancer occur between the ages of forty and seventy. The factor of age should, however, be only used with the greatest caution. Of sixty-six cases of Lindner and Kuttner, more than one-half of the patients had not reached the fiftieth year. The same can be said of Hammerschlag's cases. I have repeatedly had the experience that general practitioners have failed to recognize cancer of the stomach on account of the youthful age of the patient. Now, Wilkinson has reported a case of congenital gastric cancer, Cullingworth one in a child five weeks old, and Widerhofen a congenital cancer; Kaulich a colloid carcinoma in a boy one and a half years old. According to Schaffer, the percentage of gastric cancers in the first three decades is two per cent., according to Reichert three per cent., and according to Bräutigam 2.5 per cent. (See Inaugural Dissertation, von Reinhold Schulz, Breslau, 1886.) One fact I should like to emphasize in connection with the question of age, and that is that the limit of age for carcinoma is gradually receding.

Diagnostic Value of the Subjective and Objective Symptoms.—Among all the dyspeptic complaints, the disturbances of the appetite, thirst, the pressure, distention, and fulness, the eructation, nausea and vomiting, and the irregularities of the stool, there is nothing characteristic. Thirst is a particularly prominent and a very annoying symptom in dilatations caused by pyloric carcinoma. There is nothing characteristic about the pasty, insipid taste, nor about the coated tongue. The pains are not characteristic. The vomiting and nausea when very frequent and copious are suggestive of cancer at the pylorus or cardia. When the two openings of the stomach are free, and only the walls of the stomach are affected, there is in my experience no vomiting at all. The amount that is vomited depends on the degree of dilatation. The food is unchanged.

Significance of Blood and Hæmatemesis.—In my experience, blood is contained in the vomit in one-half of all cases of gastric cancer. Large quantities of blood are rarely vomited, but the characteristic coffee-ground vomit, in consequence of stagnation and decomposition of the blood, is diagnostically important. The more copious the effusion of blood is into the stomach, the quicker does it cause vomiting; for that reason the abundant hæmorrhages in ulcer are often vomited uncoagulated and very little altered, whereas the smaller amounts of blood in carcinoma and gastritis remain in the stomach a longer time, and then show the characteristic coffee-ground appearance. But large hæmorrhages may occur in cancer, and small hæmorrhages may occur in ulcer; and I have seen cases of coffee-ground vomiting in ulcer repeatedly.

Constipation or Diarrhœa.—In the literature of this subject, in which any reference to these points was made, I found that in 75 per cent. of cancers of the stomach there is constipation. In about 20 per cent. there is diarrhœa, and in 5 per cent. only does the stool remain regular. These figures agree with those from my clinic sufficiently to make any alteration needless. F. Müller states that diarrhœa occurs in 35.5 per cent. The greater frequency of constipation is due to the mechanical stenosis by the tumor, and motor insufficiency due to carcinomatous invasion of the muscularis.

Emaciation and Cachexia.—That these symptoms are not characteristic is evident, but they are important because the degree of emaciation will greatly influence the decision on an operation. A frequent question will be, Will the strength of this patient suffice to overcome a severe abdominal operation? The general condition gives no clew to the size of the tumor. A very minute cancer, even when it is at a place where it in no way influences the functions of the body, may depress the nutrition of the entire organism, and irresistibly lead to death. On the other hand, very large tumors on the walls of the stomach may run a long course without disturbance of the general strength and nutrition.

So in all dyspeptic symptoms there is nothing pathognostic for gastric cancer. They occur not only in other diseases of the stomach, but to a large extent in diseases of other organs. The *swelling of the cervical lymph-glands* is a very rare sign, and in my experience occurs only towards the end of the disease, by which time the diagnosis is generally clear.

Condition of the Gastric Functions.—Alterations in Secretion, Absorption, and Peristalsis. (1) The Secretion: During the development of cancer, secretion of hydrochloric acid is generally lost, so that free hydrochloric acid can no longer be detected in the test meals. Towards the end stage, both free and combined hydrochloric acid are entirely absent. It is urgently necessary to be very careful in these determinations for hydrochloric acid. A single analysis, showing sub- or an-acidity, proves nothing at all. If a first test fails to detect free hydrochloric acid, it should be repeated after allowing a longer interval to elapse subsequent to the time at which the test meal was taken. It must be borne in mind that the gastric mucosa does not secrete hydrochloric acid all over, *i.e.*, in all of its parts. Only the middle portion secretes hydrochloric acid; the pyloric region does not secrete it. Although the degree of reduction of hydrochloric acid secretion depends upon the extent and gravity of the gastritis which is caused by the carcinoma, nevertheless this may be limited to the pyloric region, where it will not interfere with the glandular apparatus which forms the hydrochloric acid. F. Mall (*Johns Hopkins Hospital Reports*, Vol. i) concludes with Heidenhain that the oxyntic or border cells in the peptic ducts are concerned in the production of hydrochloric acid, and the central cells in the production of pepsin. Now, as the pyloric region contains no border cells, a carcinoma may reach as far as the antrum pylori, a distance of from three to five inches, before it will invade the region which contains the acid or border cells. I have seen six cases in which the presence of free hydrochloric acid continued to the end of life. In two of these cases the carcinoma was seen during the operation, and in the remaining four at autopsy. These six cases had not originated on the basis of an old gastric ulcer, but were circumscribed knots of cancer, leaving the mucosa largely intact. In all carcinomas that have arisen from ulcers, free hydrochloric acid in normal or even in increased amounts may continue until death. This is sufficient evidence for the conclusion that the presence of free hydrochloric acid does not argue against cancer of the stomach. On the other hand, absence of free hydrochloric acid is no specific sign of this disease. It occurs in other gastric diseases leading to atrophy; it may occur in diseases of other organs, for instance, diseases of the kidneys, pulmonary tuberculosis, and valvular cardiac diseases, and, as I have shown (Hemmeter, "Diseases of the Stomach," second edition, page 374), free hydrochloric acid is frequently absent, though not necessarily so, in catarrhal jaundice. When free hydrochloric acid is absent, combined hydrochloric acid may still be present; and Schüle argued that the amount of hydrochloric acid deficit was an important diagnostic sign between cancerous and benign diseases of the stomach.

In determining the amount of hydrochloric acid deficit, decinormal hydrochloric acid solution is added to the filtrate of gastric contents until we get a distinct reaction with the Boas resorcin test or any of the other established tests for free hydrochloric acid. The degree of the deficit is, in my experience, no indication of the extent of the atrophy of the secreting apparatus. Very large hydrochloric acid deficits have been discovered by myself in benign diseases of the stomach. The determinations for hydrochloric acid, however, when taken in conjunction with other symptoms and signs, have a certain limited diagnostic significance.

Secretion of Pepsin and Chymosin or Rennin.—As a rule, the reduction of the secretion of these ferments goes parallel with a reduction of the hydrochloric acid secretion. For clinical purposes, the determination of the presence and strength of the pepsin secretion may be made according to the method of Hammerschläg (*Archiv für Verdauungskrankheiten,* Vol. ii, p. 4), though this method from a chemical stand-point is by no means exact. Hammerschlag used the Esbach albuminometer to determine the amount of albumen which has not been digested by the pepsin of the gastric contents. As this method is not exact when used for urinary analysis, it is less so for this purpose. Still, as a rough clinical test, it generally suffices.

Method.—A 1 per cent. solution of albumen containing free hydrochloric acid to the amount of 4 per 1000 is filled into the Esbach albuminometer to the 10 cubic centimetre mark. To this tube we add 5 cubic centimetres of the gastric filtrate to be tested for pepsin. A second Esbach albuminometer is filled to the 10 cubic centimetre mark with the standard egg albumen and hydrochloric acid solution, and as a control test 5 cubic centimetres of distilled water are added. Both tubes are now put in the incubator at a temperature of 37° F. for one hour. Then the amount of albumen in each is determined by the Esbach reagent. After both tubes have been allowed to stand quietly for twenty-four hours, the amount of digested albumen can easily be calculated in numbers expressing the percentage. This test is not sufficiently delicate to demonstrate small amounts of pepsinogen.

The reduction of the *chymosin* or *rennin* occurs in all gastric carcinomas except those arising from gastric ulcers, but very marked reduction of the amounts of both ferments is in itself not a characteristic sign for gastric cancer, because it can occur in atrophy of the mucosa from gastritis, and also from long-standing diseases of other organs.

Lactic Acid.—In 112 cases of carcinoma of the stomach, I found only three in which lactic acid was present to any considerable degree before the diagnosis could be made by other symptoms. The frequent occurrence of lactic acid in gastric cancer has been asserted by Boas to be an important diagnostic sign. The question is, Does it occur at a time to enable us to make an early diagnosis? This I must deny on the basis of a large experience with this test. Boas has admitted that excessive lactic acid in the stomach contents is not a pathognostic sign of cancer of the stomach, because it is absent in a number of cases of that disease, and may be present in gastric diseases of a benign type, and even during diseases of other organs.

Three conditions are necessary, possibly four, to bring about excessive formation of lactic acid in the stomach. These are: (1) impaired gastric motility; (2) absence of hydrochloric acid secretion; (3) reduction of albumen digestion; and, I should add (4), an impaired absorption. Lactic acid is formed in the stomach by the action of lactic-acid bacilli on the carbohydrates. Sticker has shown that the simple passage of carbohydrates through the mouth causes the formation of more or less lactic acid without exception. It is therefore necessary to give a test meal, which shall be, as far as practicable, free from lactic acid, and which shall form little of this substance during the passage through the mouth. Such a test meal has been introduced by Boas in the form of his oat-flour soup (one ounce of Knorr's oat flour boiled in a quart of water, evaporated down to one pint, and seasoned with salt only).

Lactic acid will not form in the stomach in amounts demonstrable by Uffelmann's test, even though the contents stagnate due to arrest of the peristalsis; provided the proteid digestion is still fairly good, and does not fall below 75 per cent.

Whenever there is much lactic acid in the stomach, the proteid digestion will be found to be below 75 per cent. I have made a number of chemical tests, relative to the relation of lactic acid to proteolysis, and confirmed the view that lactic acid may replace the normal hydrochloric acid in this transformation. In the contents of some carcinomatous stomachs the lactic acid was found to be in combination with the proteid of the food. When the mucosa is still capable of secreting hydrochloric acid, this will combine with the albumen sooner than the weaker acid, hence a fairly good albumen digestion signifies still a trace of hydrochloric acid and ferments. But a fairly good albumen digestion can be effected by lactic acid and pepsin in the absence of hydrochloric acid. This chemical factor merits closer investigation. Normally lactic acid, like all other soluble products of digestion, is absorbable. If, therefore, the absorption is made difficult,—which occurs especially when the contents stagnate and the hydrochloric acid secretion is depressed,—the conditions favorable to lactic-acid accumulation will be present. Whenever the movements of the stomach are normal, so that the contents can be expressed into the duodenum within six or seven hours, lactic acid will not develop to a degree that can be recognized by the ordinary tests, although the hydrochloric acid secretion has been lost entirely. Hammerschlag took such a gastric chyme containing no hydrochloric acid, but from stomachs with normal motility, and added the third necessary factor, viz., stagnation, by letting it stand at room temperature. Under such stagnation lactic acid rapidly developed in the chyme. In gastric carcinoma we have the conditions favorable to lactic-acid formation in the majority of cases; *vide* suppression of hydrochloric acid, stagnation of contents, impaired proteid digestion, and impaired absorption, so that lactic acid is found most frequently in cancer of the stomach. Rosenheim found it in 78 per cent., Lindner and Kuttner found it in 60 per cent., Strauss found it in 91 per cent., and I have found it in 82 per cent. of all my cases of gastric cancer. But the conditions necessary to its formation in the stomach can be brought about by diseases other than cancer; for instance, in benign pyloric stenosis, in atrophic gastritis with motor insufficiency; and even in diseases of other organs. I have discovered lactic acid in the stomach in marked excess when the stomach itself was not affected; but the impaired peristalsis was caused in one case by a pancreatic cyst, in another by a carcinoma of the gall-bladder, and in a third case by a large gall-stone. These conditions had caused compression of the duodenum effecting obstruction to the outlet of gastric chyme with a subsequent gastritis, the latter most probably causing the loss of hydrochloric acid secretions. In still another case in which there was a compression of the duodenum by floating kidney, the presence of lactic acid was only transient. Whenever the kidney could be retained in place by a proper bandage, the stomach resumed its secretions partially, and the peristalsis was to a degree resumed, and the lactic acid, except in minute traces, disappeared from the contents. Lactic acid, then, although it is not an early sign, is a clinically important sign. It means absence of hydrochloric acid, stagnation, and reduction of the digestive ferments and loss of absorption; conditions which are most frequently found in cancer, and therefore the presence of lactic acid, although not a pathognomonic sign, nevertheless, when it occurs in conjunction with other symptoms, should suggest the probability of cancer. The test necessary for this which is most practical is the one originally suggested by Uffelmann. The reagent consists of 10 cubic centimetres of a 4 per cent. solution of carbolic acid, 20 cubic centimetres of distilled water, and one drop of the liquor of the sesquichloride of iron. This gives an amethyst-blue solution. The presence of lactic acid changes this to a yellowish green. The reagent is sensitive to 0.5 per 1000 of lactic acid, which amount is always pathological and of diagnostic significance. Tests more sensitive than this would not be useful clinically. Boas (*Deutsche medicinische Wochenschrift*, 1893, No. 39) has given an exact method for quantitative determination. Strauss (*Berliner klinische Wochenschrift*, 1895, No. 37) has devised a practical little funnel for separating the lactic acid by agitation with ether (for illustration, see Hemmeter's "Diseases of the Stomach," second edition, page 168).

Microscopical Examination of the Stomach Contents.—There are only two structural elements in the stomach contents that have a possible diagnostic significance. These are: (1) tissue fragments, minute portions of the neoplasm; (2) the so-called Oppler-Boas bacilli. The tissue fragments are of undoubted diagnostic value if they contain structure of the neoplasm. The question is, Do they occur early enough in the disease to make a timely diagnosis possible? It is probable that the fragments are only detached from ulcerating tumor masses in the stomach, such as have already developed metastases; but I shall describe a method, that of curetting the walls of the stomach with a soft tube, and thereby loosening the superficial epithelium at a time when the neoplasm is not yet ulcerating. These fragments can be washed out of the stomach by lavage and sedimented in the electric centrifuge. I have used this method in forty-eight cases of gastric carcinoma, and I regard it as eminently important and adapted to early clinical diagnosis. I wish to emphasize that not only fragments of the neoplasm itself are to be sought after, but any cellular tissue that is found should be carefully stained and studied. The most remarkable feature of the sediment from such a stomach, after this so-called curetting, is a large number of cells presenting karyokinetic figures. Rieder (*Deutsche Archiv für klinische Medicin,* Band liv, Heft 6, p. 544) reported a case in which he made a diagnosis of malignant disease of the peritoneum and pleura from finding numerous cells in the exudates, showing indirect and atypic nuclear division. Mitoses occur very frequently. The forms of cell and nuclear division known as the equatorial plate and the monaster are frequent. Another form known as the anaphase, which in normal karyokinesis precedes the formation of the daughter stars, and leads up to the formation of resting daughter nuclei, I have observed three times in the curettage from stomachs at a stage when there was no tumor palpable, and in which the diagnosis was confirmed by operation, autopsy, or by the later development of a tumor. The presence of a large number of cells in the stomach after curetting with the stomach-tube, which cells show mitosis, and some of them pathologic or asymmetric mitosis, is very significant, and should stimulate further and very careful examination. Sooner or later a fragment will be obtained which will give the typical structure of carcinoma. For this kind of curetting a soft stomach-tube suffices, provided it has a lower and a lateral aperture, the edges of which scrape away the tiny elevations of gastric mucosa when the tube is moved in and out of the mouth. The procedure should be carried out in the morning before breakfast, when the stomach is empty. This method of obtaining specimens from the gastric mucosa during life is free from danger, and not once in my experience has any pain, distress, or hæmorrhage been produced thereby. In many cases of chronic gastritis, achylia gastrica, and carcinoma, tissue fragments are found in the lavage water without especially making an effort to loosen them, by moving the tube along the gastric walls.

The forcible detachment of larger pieces of gastric mucosa is an accident occurring during lavage by suction or aspiration of the tube, particularly when the instrument is in inexperienced hands. It is followed by copious hæmorrhage, yet pain is rarely complained of. I reported a case of one of my students (Hemmeter, "Diseases of the Stomach," second edition, p. 146), who aspirated a piece of his own gastric mucosa 10 by 4 millimetres; it was followed by a profuse hæmorrhage but no other serious consequences, as uninterrupted recovery occurred under rest and liquid diet.

The Oppler-Boas bacilli are very long, rod-shaped organisms, non-motile, and usually thicker at one end than at the other, presenting the shape of a base-ball bat. Kaufmann and Schlesinger (*Wiener klinische Rundschau*, 1895, No. 15) have isolated these organisms, and asserted them to be of great significance in cancer of the stomach. Riegel ("Erkrankungen des Magens") confirms the occurrence of these bacilli in enormous numbers in carcinoma, and adds that, although there are numerous fungi that have the property of forming lactic acid in stomach contents, this cannot alter the significance of the Kaufmann and Schlesinger observation. He does not consider these organisms as pathognomonic of gastric cancer, but as very important for the diagnosis. Dr. Harry Adler and myself have examined fifty-six cases for the Oppler-Boas bacilli, and failed to observe them in only three cases. The presence of this organism is therefore an important factor, aiding in the diagnosis; and whilst not pathognomonic, they are of the same diagnostic value as the presence of lactic acid, and therefore do not constitute an early sign of cancer.

Microscopical Evidences gained from the Contents or the Walls of the Stomach.—In the preceding I have briefly outlined my opinion concerning the diagnostic value of subjective and objective signs and symptoms; of the various ways and degrees in which the three functions of the stomach, peristalsis, secretion, and absorption, can be altered; the value of the chemical and microscopical examinations of the urine, blood, and gastric contents. There is therefore not one clinical sign or symptom, chemical or microscopical evidence, which is characteristic or pathognomonic for the fully developed gastric carcinoma, not to speak of the value of these conditions and symptoms for the *early* diagnosis. We are therefore compelled to seek further evidences from which we may hope to obtain information. One of the first and indispensable steps towards the attainment of new truth is to admit the helplessness of our present knowledge, and the inadequacy of our present means of diagnosis. I have attempted to enlarge the diagnostic technique in this respect by efforts at obtaining histological fragments of gastric mucosa by curetting the walls of the stomach with a stomach-tube ("Histological Studies relating to the Early Diagnosis of Carcinoma of the Stomach," *Philadelphia Medical Journal*, February 3, 1900, p. 279). After this curetting the stomach is washed out with a measured quantity of water. If the particles detached from the gastric mucosa are not visible to the naked eye, this lavage water is sedimented in the centrifuge and the sediment examined microscopically. It is not sufficient to simply look for particles of the actual structure of the malignant tumor in the wash-water. One may occasionally have the good fortune to arrive at a positive diagnosis by finding actual structural fragments of an existing carcinoma, but in my experience such an occurrence always speaks for a neoplasm that has already progressed very far, and which can be diagnosed by other methods, without gastric curage. Structural fragments are only detached from ulcerating tumor masses in the stomach, and in all the cases in which I succeeded in getting such fragments, metastases had already formed, and the diagnosis could not be called an early one. The finding of actual tumor masses, then, is comparatively rare, and while it firmly establishes the diagnosis of carcinoma of the stomach, is of no value to the surgeon in his efforts to secure an early operation. In curetting a very large number of stomachs, for the purpose of studying the histological condition of the mucous membrane, I have been led to hope for some aid to an early diagnosis by a study of the pathologic and atypic mitoses that occur in the gastric structure. The finding of pathological mitoses, and even of carcinomatous particles, is considered an accident by a number of competent observers; but it is probable that this occurrence is said to be so rare, not because these fragments do not occur in the vomit or wash-water, but because they are not methodically and systematically looked for, and especially because few well-directed efforts have been made by competent men to detach such fragments intentionally from the gastric mucosa. There is every reason why we should intentionally attempt to secure such particles from the stomach, just as they are secured by curetting the uterus. Hitherto, in such examinations, the histologist reserved his opinions, as a rule, until he found the typical structure of a carcinoma in the tissue fragments gained. But it is possible to go a step farther, and to diagnose this disease from fragments showing the following conditions. (*a*) The ducts of the peptic glands are elongated and dilated, the cells frequently detached from the periphery of the gland, and lying loose in the gland lumen and presenting numerous karyokinetic figures. (*b*) When these nuclear figures, or mitoses, present asymmetric or hypochromatic and hyperchromatic forms, they are especially suggestive of a malignant process. These mitoses must be examined in tissue that is as fresh as can be obtained; where the least decomposition had taken place, they are no longer demonstrable by tinctorial methods. For this purpose curage of the stomach is indispensable, as the tissue fragments gained by other methods, vomiting or simple lavage, are, as a rule, in a state of necrobiosis.

The result of the procedure of curage is made more reliable if the patient is fed by the rectum for a time, and all food excluded from the stomach. Wherever possible, the stomach should be thoroughly washed out for several days in succession, in order to avoid confounding particles of meat, etc., retained in the ingesta, with particles of neoplasm. The diagnosis of malignant disease of the peritoneum and pleura from numerous cells found in the aspirated exudate, which cells were in the state of indirect nuclear division, was probably first definitely made by Rieder (*Deutsche Arch. f. klin. Med.*, Band liv, S. 544). The autopsy in Rieder's case proved the existence of a sarcoma of the peritoneum secondary to malignant disease of the ovaries. In the fluids obtained during life cells were found which were remarkable, in the first place, on account of the differences in size and shape of the individual cells. Often there were indentations and constrictions, sometimes buddings. In many cells there were one or many vacuoles, often so large that the nucleus was pushed to one side, and sometimes almost completely submerged beneath the enormous vacuole. Examination of the stained cells showed a large number of cells in a state of indirect division, and especially cells with atypic mitoses. Geo. Dock ("Cancer of the Stomach in Early Life," *Amer. Journal of Med. Sciences*, 1897, p. 65) made similar studies and established the diagnosis of carcinoma of the pleura and peritoneum from analogous cellular forms found in the aspirated transudate. Asymmetric mitosis is not easy to recognize in fragments gained from the gastric mucosa on account of the frequent imperfect preservation of the chromosomes in many cases. Many fragments are found which are useless for the purpose of studying pathologic mitoses for this reason. The methods and technique are fully described in my text-book on "Diseases of the Stomach," second edition, pages 561 to 564.

In a number of German publications, I have noticed the definition of EARLY diagnosis, to the effect that the disease is

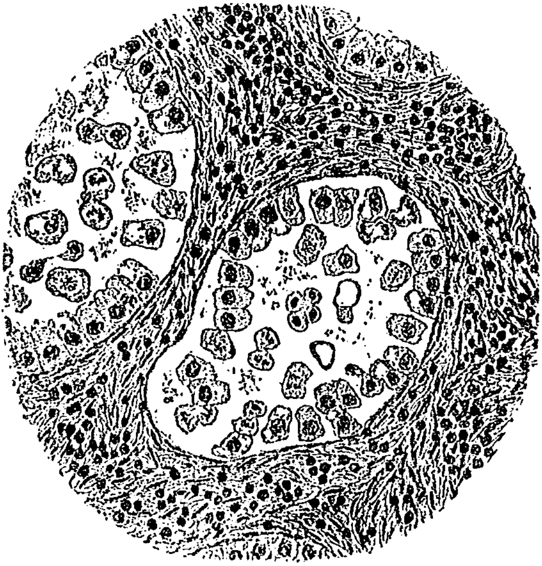

FIG. 1.—Fragment of gastric mucosa obtained by curage from case O. A. B., showing lumen of two gland tubules. The interglandular connective tissue is thickened and permeated with small, round-celled infiltration. The greater portion of the epithelium of the gland is detached; many cells show vacuoles, some of them so large as to submerge the identity of the original cell, which appears either as a small rim of protoplasm around a vacuole, or as a smaller mass at the side of a huge vacuole. Numerous gland cells in the state of atypical mitosis, there are in both glands lumens, asymmetrical mitoses, some with disrupted chromosomes. In the centre of one lumen is a four-lobed cell presenting four nuclei. Asymmetrical mitoses do not derive their name from asymmetry in shape or configuration; an asymmetrical mitosis is one whose daughter stars do not contain a like or even number of chromosomes.

recognized before a tumor can be felt. As fully two-fifths, according to some authors, one-half, of the tumors of the stomach are not palpable, it is evident that this is not a reliable sign to go by. Tumors may be very large, and not at all be palpable. The palpability of gastric tumors depends too much upon the situation of these neoplasms in the stomach; although 60.8 per cent. of the tumors observed at autopsies by Wm. H. Welch (Pepper's "System of Medicine," Vol. ii) were situated in the pyloric region, all of these tumors are not palpable. It is only when the normal pylorus is displaced downward by the weight of the tumor that it becomes palpable. I have observed quite a number of tumors of the pylorus at autopsy which were by no means palpable during life, owing to the fact that the tumor was adherent to the under surface of the liver.

In an investigation on the pathologic anatomy of the human stomach with a special reference to the practical value of diagnosis by means of fragments of the mucous membrane, Leuk (*Zeitsch. f. klin. Med.*, Band xxxvii, Heft 4) holds that it is not possible to distinguish between carcinoma and atrophic gastritis by examining such fragments unless portions of actual carcinomatous growth are found. He does not go into the consideration of the relative frequency of the findings of cells showing atypic and asymmetric mitoses in the contents of the stomach or gained after gastric curage. But few investigators have as yet worked over this subject, as may be seen from the literature in my articles (*Phila. Med. Journ.*, Feb. 3, 1900, and *N. Y. Med. Record*, Oct. 21, 1899, and in the second edition of my text-book on "Diseases of the Stomach"). The whole subject is not sufficiently mature to permit of the annunciation of dogmatic conclusion either way. I wish simply to emphasize that the diagnosis of carcinoma of the stomach *has* been made in this way, at a time when we had every good reason to believe that it was an early diagnosis, and that this opinion was confirmed either at operation or at the eventual autopsy. Leuk's work, in my opinion, is not based upon a sufficiently large number of clinical observations, as might be desirable for the importance of this question. It is confessedly

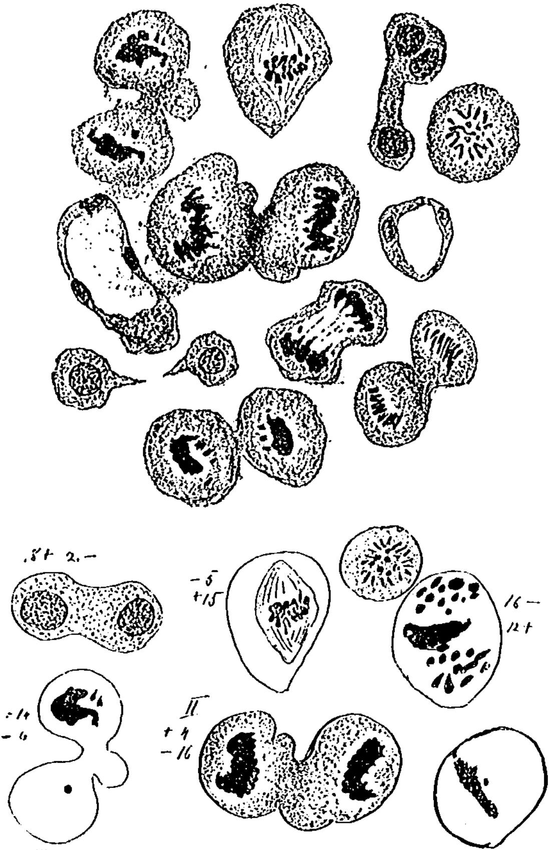

FIG. 2.—This gives a number of cells in the state of atypical mitoses, taken from parts of the specimen illustrated in a lower power on Fig. 1. To the left side, above the centre, is a mitotic form showing a cell with a huge vacuole and three nuclei; directly opposite on the right side of the drawing is a similar smaller cell in which the protoplasm has surrounded a vacuole like a narrow ring. The lowest cell in the figure is an asymmetric mitosis, showing an uneven number of chromosomes and disrupted chromosomes. This is also shown in other cells of the illustration, particularly in the cells showing a crippled pithode stage. The cells thus pictured were discovered lying detached in the lumen of the gland-ducts as shown in Fig. 1.

a rare thing that the diagnosis of carcinoma of the stomach at an early stage can be made in this manner; but this I explain on two grounds: (1) It is rare that patients present themselves at an early stage for examination; and (2) the method of gastric curage is rarely practised. I am of the opinion that, as the method comes more and more into usage, we may hear of a larger number of early diagnoses of this disease being made.

Wherever appreciable quantities of lactic acid are regularly found in the stomach, together with the signs stated in the preceding, the matter of an EARLY diagnosis is out of the question. The presence of tumor or metastases, the presence of considerable quantities of lactic acid and Oppler-Boas bacilli, the reduction of the proteid digestion under 30 per cent., with absence of free hydrochloric acid, mean a late diagnosis from the surgical stand-point.

The test of the peristalsis or motility of the stomach should never be omitted from the diagnostic methods. In the majority of cases the peristalsis suffers greatly, but in cancers located at the fundus and at the curvatures the motor power of the stomach may remain normal throughout the course of the disease. There are even rare cases of pyloric cancers in which motor power may remain intact for a long time.

Absorption.—The tests for the absorptive power of the stomach usually give evidence of great reduction in this function. There are, however, many exceptions to this rule, no doubt due to the fact that the gastric mucosa is in a fairly normal condition, notwithstanding the presence of a very circumscribed carcinoma.

Urine.—Investigation made hitherto on metabolism and the constituents of the urine have, in my opinion, not as yet yielded any results of practical value for the diagnosis Albumen is present in from 35 to 50 per cent. of the cases according to F. Müller. Excess of indican is present in from 85 to 90 per cent. of the cases.

Blood Examinations.—These have shown a reduction in the percentage of hæmoglobin and absence of the digestive leucocytosis. Frederick P. Henry has emphasized the fact that in gastric carcinoma the red corpuscles number 2,000,000 to 3,000,000 per cubic millimetre, whereas in pernicious anæmia, which most resembles cancer of the stomach, the count is much lower, sometimes less than 500,000 (*Archiv für Verdauungskrankheiten,* Band iv, S. 1). This phenomenon will serve to distinguish these two diseases.

The number of erythrocytes is not proportionate to the degree of cachexia. In this opinion Henry has been confirmed by Dr. Anton Krokewicz (*Archiv für Verdauungskrankheiten,* Band vi, p. 25). My personal experience is that the numerical relations of the cellular elements of the blood are too variable to constitute a reliable diagnostic factor in gastric carcinoma.

Tumor.—Demonstration of a tumor in the stomach is the most reliable evidence upon which to base a diagnosis, but it is not an early diagnostic sign. According to various prominent German surgeons, the presence of a tumor is a contraindication to the execution of a radical operation having in view the total extirpation of the neoplasm. Czerny and Rindfleisch (Festschrift gewidmet Theod. Billroth, 1892) and Kraske (*Berliner klinische Wochenschrift,* 1894, Nos. 20 and 21) argue that gastric cancer should not be radically operated upon after it can once be diagnosed in the form of tumor. It will not be necessary for me, in this short article, to consider the methods of palpation and the mobility of gastric tumor, but I should like to recommend urgently the palpation of the patient, either in a warm bath or under anæsthesia, when a tumor cannot be made out by palpation under ordinary conditions.

Hypertrophic Stenosis of the Pylorus—Stenosing Gastritis.—The differential diagnosis between this condition and carcinoma is difficult. W. S. Thayer and Rosenheim have reported cases of benign stenosis that could not be distinguished from carcinoma. A history of very long-standing dyspeptic disease, with alternating improvements and aggravations, speaks for hypertrophic stenosis if the symptoms and anamnesis of chronic gastritis accompanied the development of the stenosis. The presence or absence of tumor is of no diagnostic value in differentiating these two conditions. A tumor when present may as well be a benign hypertrophy as a cancer. Repeated and consecutive weighing of the patient is urgently indicated in benign hypertrophic stenosis; there will be more frequent and more lasting improvements, extending sometimes through years. Motor function and stagnation grow progressively worse in carcinoma; in benign stenosis they are amenable to treatment by lavage and diet.

In stenosis due to cicatrix from gastric ulcer there will have been a history of blood in the vomit or stool and presence of excess of hydrochloric acid in the gastric chyme; if the stenosis is due to hypertrophic gastritis, these signs will not be observed, though normal amount of hydrochloric acid may exceptionally be met with in the early stages of the latter.

Among all the early signs and symptoms of gastric carcinoma, the dyspeptic symptoms and the evidences of disturbed functions, and the general condition, there is not one fact that is pathognostic for an early diagnosis. I do not assert, however, like Haberkant, Lindner, and Kuttner, that in the present state of our knowledge the early diagnosis of gastric carcinoma is entirely impossible.

Diseases of the Stomach associated with the Absence of Hydrochloric Acid.—A brief consideration of these will be indispensable in our efforts to reduce the possible sources of error in making a diagnosis. The atrophies that may be associated with the absence of hydrochloric acid are the following: 1. Apparently idiopathic (Nothnagel and Fenwick). 2. End stages of long-standing chronic gastritis. 3. Gastric atrophies occurring with mammary, uterine, and intestinal carcinoma. 4. With benign pyloric stenosis. 5. With gastric cancer.

Achylia gastrica, which has been first described by Einhorn in 1888, means the complete absence of the secretion of gastric juice, not simply of the hydrochloric acid only, but also of the ferments. So-called anacidity, or achlorhydria, means the absence or loss of hydrochloric acid, but pepsinogen and rennin zymogen are still secreted. Achylia gastrica may be congenital. The existence of so many conditions connected with the absence of hydrochloric acid is an evidence of the difficulty of utilizing this sign for diagnosis. In Groups 1 and 2, however, the motility is normal; there is, as a rule, no lactic-acid formation, and the course of the disease is generally a long one. The atrophies described by Fenwick under Group 3 have not been as yet carefully studied with regard to their motility and the presence or absence of lactic acid. Group 4, the benign forms of pyloric stenosis are very rare, but they can be distinguished by their long, slow course. If, therefore, the history extends over several years, no importance can be attached to the presence of lactic acid. Achylia gastrica is also a disease of long duration; the motility is always excellent, the appearance of the patient is good, and the condition of the chemistry of the stomach is always the same, showing no lactic acid, no ferments, and no hydrochloric acid.

Neurosis of the Stomach associated with Permanent or Temporary Loss of Hydrochloric Acid Secretions. These conditions are very often perplexing, and might be confused with the diagnosis of cancer, but the presence of hysteria or neurasthenia and the long duration of the disease, together with the result of curetting of the stomach for fragments of mucosa, should make the differentiation possible. Patient observation will eventually detect a period in the course of neuroses when hydrochloric acid is again secreted normally. A neurosis during the course of which a perfectly normal secretion may alternate with anacidity (even achylia), and on the other hand with hyperacidity or supersecretion, was first thoroughly investigated at my clinic. I have proposed the name Heterochylia for this condition.

Gastroscopic Examination.—Whether the gastroscope will enable us to make an early diagnosis of gastric carcinoma is a very remote problem. Gastroscopy has no doubt made distinct advances during the last ten years, but it is connected with so many difficulties and dangers that the general application of this method cannot be hoped for at present. Mikulicz, Kelling, Rosenheim, Revidzoff, and Kuttner have published their studies on gastroscopic examination of the stomach. After a critical study of their reports, one cannot fail to be conscious of discouragement at the absence of practical results. There is still very little promise in this method.

Electrodiaphany or *Transillumination* of the stomach, according to the method first suggested by Einhorn, may give a suggestion of the existence of a tumor of the anterior gastric wall. But a chance of such a demonstration will be very small. Out of 1300 cases of cancer of the stomach collected by W. H. Welch (Pepper's "System of Medicine," Vol. ii, p. 561), only thirty occurred on the anterior wall, *i.e.*, 2.3 per cent. In order to cut off the rays of the intragastric lamp, a tumor must have a thickness of 1.5-2 centimetres. (Kuttner and Jacobson, "Experiments on Cadavers," *Berliner klinische Wochenschrift*, 1893, No. 89.) These observations have been confirmed by the writer. With a tumor of such dimensions as a requisite, and the extreme rarity of the location of tumors on the anterior gastric wall, I am disposed to consider this method unavailable for the early diagnosis.

The Use of the X-Ray for Diagnosis.—The author was among the first to publish studies of the position and size of the stomach for diagnostic purposes (see *Boston Medical and Surgical Journal*, April, 1896). Boas and Levy-Dorn (*Deutsche medicinische Wochenschrift*, 1898, No. 2) have proposed a method of recognizing strictures of the gastro-intestinal canal by skiagraphy. Capsules coated with an insoluble material and filled with bismuth subnitrate cut off the X-rays, and their position can be recognized in the intestines; but I doubt very much whether this method will exactly locate a carcinomatous constriction, because the intestine is not a simple tube, but a labyrinth of convolutions, superimposed upon each other, so that, even if the bismuth capsule could be recognized, it is absolutely impossible to state whether it is in the stomach or in the intestines, or in what convolution of the intestine it is located.

Exploratory Laparotomy.—This diagnostic incision I would warmly recommend in all cases of gastric disease associated with (1) rapid emaciation; (2) absence of hydrochloric acid; (3) reduction of proteid digestion under 30 per cent.; and (4) presence of lactic acid by Uffelmann's test or (5) of numerous long baseball-bat shaped Oppler-Boas bacilli. If all of the above signs and symptoms are present in any case, even of short standing and recent beginning of the disease, and no improvement follows three weeks of appropriate treatment, I should feel justified in making the diagnosis of carcinoma of the stomach even in the absence of tumor, and urge an exploratory laparotomy.

Albert Albu (*Archiv für Verdauungskrankheiten,* Band iv, p. 466) reports a very interesting case in which the exploratory laparotomy revealed an infiltration of the pylorus, which, in his own words, was no thicker than a small chestnut, and proved, after a resection of the pylorus, to be scirrhus. This case had an acute attack of tetany. Recovery after pylorectomy was satisfactory, and the motor function of the stomach restored. In this case the diagnosis was not certain before exploratory laparotomy had been undertaken. The early diagnosis and early operations are extremely rare in the literature of the subject, due to the reasons which I have already stated, viz., that the patients do not present themselves in time, and that the methods which are most promising for an early diagnosis are either neglected or permission for their execution refused by the patient. The most important information from all the physical signs and symptoms, and from the chemical and microscopical investigations, may be arranged in order of their diagnostic value as follows (but I do not desire to be dogmatic in this statement):

(1) Chronic gastritis or nervous dyspepsia with progressive aggravation in spite of proper treatment.

(2) Progressive weakening of the peristaltic power. This can only be confused with the benign stenosis of the pylorus, but in the latter case (the benign stenosis) there is always a normal or an excessive amount of hydrochloric acid. In malignant stenosis there is absence of hydrochloric acid and formation of lactic acid. The diagnosis between benign and malig-

nant stenosis may be difficult at the beginning of the clinical observation of any case, but after two to four weeks of observation should present no difficulties.

(3) Progressive diminution in the amount of free hydrochloric acid with steady loss of peristaltic power.

(4) Persistent absence of free hydrochloric acid and the presence of abundant atypic and asymmetric mitoses after gastric curage, together with other signs of inflammation. (*Philadelphia Medical Journal,* February 3, 1900.)

With such clinical indications exploratory laparotomy should be undertaken, and where this step proved the diagnosis to be wrong, in my experience, it was discovered that conditions were present which necessitated operative interference anyway, such as, for instance, motor insufficiency from cicatrices, indurated ülcers, or adhesions.

In this schema the diagnostic value of the Oppler-Boas bacilli, tumor, lactic acid, are not referred to, because they are late signs. I do not wish to be understood, however, that a surgical operation should not be undertaken when these late signs are present. Many times even the presence of a tumor is not a contraindication to an operation, because a malignant tumor in the stomach may be present, as I have noted on three occasions, and no signs of metastases or infection of the lymph glands discoverable by a careful search at the autopsy.

The diagnosis of carcinoma of the stomach is still in its elementary rudiments. We do not know what the causes and nature of malignant neoplasms are. The diagnosis of any disease under such conditions must be difficult. We must bear in mind that the diagnosis on neoplasms on the surface of the body in their early stages presents considerable difficulty, and in case of the stomach we are required to diagnose these new growths in an organ entirely hidden from view, and almost entirely from touch. With a knowledge of the nature and cause of the disease will come a knowledge of its early recognition and its successful treatment. Think of the condition of the diagnosis of diphtheria and tuberculosis before the cause of these diseases was understood. But from many sides and in many countries dutiful laborers are working towards the common goal of the cause of this human scourge. Then will come the time where the malignant neoplasm will melt away under the influence of a new treatment, similarly as the pseudomembrane disappears in diphtheria after the injection of antitoxin. There is some reason to believe that not all malignant neoplasms have the same etiology, and therefore will probably not have the same treatment. Recent personal studies have led me to incline to the view that in some carcinomas, at least, we are dealing with a deep-seated disturbance of the innermost metabolism of the individual cells, and that whatever bacteriologic findings can be made in such growths, are of secondary importance or accidental accompaniments. The further development of the subject depends, in my opinion, not so much on bacteriologic investigation as upon the pathologic and physiologic chemistry of the cell; though the problem as yet presents great difficulties, still, they do not seem unsurmountable, even with the means at present at the disposal of the physiologic chemist.

The inevitable recurrence of carcinoma after operation of gastric malignant neoplasm should impress us with the fact that surgical operation cannot be the treatment of the future for such diseases. The impression is spreading that gastric surgery can, after all, only bring symptomatic relief, and, according to the classical testimony of Mikulicz (Chirurgischer Congress, 1896) gastric surgery, after a career boldly and brilliantly begun, has arrived at the height of its capability for technical development after twenty years, and now stands arrested before the natural boundaries of internal medicine, the fundamental pillars of pathology. It does not appeal to reason to assume that this form of treatment, by operation merely, although it is at present the most satisfactory and promising that we possess, represents the limit of human knowledge and ingenuity. The Löffler, Behring, Pasteur, Koch, and Virchow of the future will solve this riddle for us, and the obscurity about malignant neoplasms must vanish before human intellect, and then will come an effective treatment based upon the etiology of the disease. "Life is short, but Art is long." Hippocrates: *Ὁ μὲν βίος βραχὺς ἡ δὲ τέχνη μακρά.*